Resting State Functional Connectivity Correlates of Different Aggression Subtypes in Children and Adolescents with Disruptive Behavior

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“When you change the way you look at things, the things you look at change.” (W. Dyer)

Contents

Summary

Clinical manifestations of severe aggressive behaviors in children and adolescents include DSM-diagnoses of conduct disorder (CD) and oppositional defiant disorder (ODD). CD characterizes frequent major violations of rules, norms, and rights. ODD manifests as pattern of angry, argumentative, and vindictive behavior. There is a considerable body of behavioral research on several aggression subtypes including reactive (RA) and proactive (PA) aggression along with callous-unemotional (CU) traits. However, knowledge of functional neural correlates at rest is limited. The majority of studies of resting state functional magnetic resonance imaging to date restricted analyses to male adolescents with CD. Additionally, RA, PA, and frequent comorbid symptoms, particularly anxiety levels, have been neglected. This dissertation aimed to fill these gaps by investigating A) seed-to-voxel cluster and B) whole-brain voxel-to-voxel resting state functional connectivity (rsFC) in 207 children and adolescents, of which 118 were cases with aggressive behavior in the clinical range including diagnoses of CD and/or ODD and 89 healthy controls, and considering RA and PA aggression subtypes along with CU traits. The present PhD project is embedded in the framework of the European multi-center FP7 projects Aggressotype and MATRICS.

In the first study, we investigated seed-based rsFC in cases compared to healthy controls, and aggression subtype-specific connectivity within cases. Recent studies reported mainly reduced rsFC in male adolescents with CD compared to healthy controls. CU and CU-related traits have been associated with predominantly increased rsFC. Affected brain regions include the posterior cingulate cortex (PCC) as part of the default mode network (DMN) and the amygdala and the anterior insula belonging to the salience network (SN). Using a common seed-based approach, regions of interest were defined in the anterior medial prefrontal cortex (amPFC) and PCC as core

regions of the DMN and in bilateral amygdala and bilateral anterior insula as parts of the SN. Compared to healthy controls, cases demonstrated reduced DMN (PCC seed) and – after controlling for ADHD symptoms – reduced SN (left anterior insula) connectivity with left hemispheric frontal clusters. Within cases, higher RA and PA scores correlated with increased connectivity in brain areas previously implicated in emotion, empathy, and cognitive control, such as the precuneus and the right caudate nucleus. All CU subdimensions correlated positively with several DMN and SN seed-based rsFC to clusters including precentral gyrus, precuneus, and cerebellar regions. These areas have been linked to emotion, empathy, moral, and self-referential processes. This first study thus revealed aggression subtype-specific rsFC patterns, extending the knowledge of neural networks involving two core regions implicated in aggression-related disorders to distinct forms of disruptive behavior in children and adolescents.

In the second study, we extended previous efforts by investigating unrestricted graph theory based whole-brain voxel-to-voxel rsFC. By calculating the Intrinsic Connectivity Contrast (ICC) as global connectivity strength of each voxel with all other voxels, we measured changes in network centrality. Additionally, analysis of Integrated Local Correlation (ILC) examined changes in local coherence by integrating voxel-wise spatial correlations. Besides ADHD symptoms, co-occurring anxiety levels were considered. Cases showed altered rsFC including the medial frontal cortex compared to controls, but only when anxiety and not ADHD symptoms were controlled for. Importantly, most of the aggression subtype-specific voxel-wise rsFC patterns within cases depended on the additional control of both ADHD and anxiety symptoms. Both RA and PA symptoms related to connectivity alterations including parietal areas and distinct connectivity patterns in central gyrus and precuneus, which seem to be involved in aggression, emotion, and cognitive control-related processes. CU traits correlated with patterns including temporal and cerebellar areas implicated in empathy, emotion, and reward-related activity. This hypothesis-free rsFC study further supported an aggression subtype-specific approach and underlined the crucial role of considering comorbid symptoms in such analyses.

In summary, this dissertation project points to the sensitivity of rsFC to developmental forms of aggression, and to the importance of considering different manifestations of aggression in children and adolescents with disruptive behavior. Firstly, both seed- and unrestricted voxel-based whole-brain analysis approaches showed alterations in rsFC including frontal brain areas in cases compared to healthy controls, which partly depended on the additional control of either ADHD or anxiety symptoms. Secondly, both analysis approaches revealed altered and predominantly distinct rsFC related to RA and PA subtypes along with CU traits within cases. Importantly, comorbid ADHD and anxiety symptoms were crucial in identifying aggression subtype-specific voxel-wise rsFC alterations. Taken together, the significant aggression subtype-specific seed-based and voxel-wise rsFC results in a large sample of children and adolescents with aggression elucidated that distinct though overlapping brain connectivity measures can disentangle distinct forms of aggressive behaviors and underline a dimensional rather than categorical approach. Our results could have clinical implications, as they might provide support for personalized diagnostic and treatment of aggression-related disorders tailored to the specific neural manifestation of aggressive behavior.

Zusammenfassung

Schwerwiegend aggressives Verhalten von Kindern und Jugendlichen kann anhand von DSM-Diagnosen wie der Störung des Sozialverhaltens (CD) und der Oppositionellen Störung des Sozialverhaltens (ODD) klinisch erfasst werden. CD beschreibt wiederholte erhebliche Verletzung von Regeln, Normen und Rechten. ODD zeigt sich anhand von wütenden, streitsuchenden und rachsüchtigen Verhaltensmustern. Von zentraler Bedeutung sind dabei einige Subtypen von Aggression wie reaktive (RA) und proaktive (PA) Aggression sowie verschiedene Ausprägungen eingeschränkter prosozialer Emotionalität (CU-Traits). Während es auf Verhaltensebene immer mehr Forschung zu diesen Aggressionsformen gibt, ist das Wissen über funktionelle neuronale Korrelate während des Ruhezustandes noch begrenzt. Bis heute beschränkten Studien über den Ruhezustand des Gehirns, gemessen mit funktioneller Magnetresonanztomographie, ihre Analysen meistens auf männliche Jugendliche mit CD. Ausserdem blieben RA, PA sowie komorbide Symptome, vor allem Ausprägungen von Angst, bislang unbeachtet. Diese Dissertation setzte sich das Ziel, ebenjene Forschungslücken zu schliessen. Wir untersuchten demzufolge A) seedbasierte funktionelle Konnektivitäten im Ruhezustand (rsFC) und B) rsFC einzelner Voxel mit allen übrigen Voxeln im Gehirn von 207 Kindern und Jugendlichen. Dabei zeigten 118 Studienteilnehmende ausgeprägtes aggressives Verhalten mit Werten im klinischen Bereich und hatten zumeist auch Diagnosen von CD und/oder ODD erhalten. 89 waren gesunde Kontrollprobanden. Wir berücksichtigten RA und PA Aggressionssubtypen nebst CU-Traits. Das vorliegende Dissertationsprojekt ist in die europäischen Multicenter FP7-Projekte Aggressotype und MATRICS eingebettet.

In der ersten Studie wurden Unterschiede zwischen aggressiven und gesunden Kindern und Jugendlichen hinsichtlich seedbasierter rsFC

untersucht, und ob sich diese abhängig von der Aggressionsform innerhalb der aggressiven Gruppe unterscheidet. Bisherige Studien berichteten vorwiegend reduzierte rsFC bei männlichen Jugendlichen mit CD im Vergleich zu gesunden. CU- und CU-ähnliche Traits wurden mit meist erhöhter rsFC in Verbindung gebracht. Zu den betroffenen Gehirnarealen zählen der posteriore cinguläre Cortex (PCC), der zum Default-Mode-Netzwerk (DMN) gehört, sowie Amygdala und anteriore Insel, Bestandteile des Salienz-Netzwerks (SN). Mittels der verbreiteten seedbasierten Herangehensweise wurden Bereiche von Interesse im anterioren medialen Präfrontalkortex (amPFC) und im PCC (Kernregionen des DMN), sowie in bilateraler Amygdala und bilateraler anteriorer Insel (Bestandteile des SN) erstellt. Verglichen mit den gesunden zeigten die aggressiven Kinder und Jugendliche eine verringerte Konnektivität mit linkshemisphärischen frontalen Clustern, zum einen mit Bereich von Interesse im DMN (PCC seed), zum anderen nach Kontrolle für ADHS-Symptome im SN (linksseitige anteriore Insel). Innerhalb der aggressiven Studienteilnehmenden korrelierten höhere RA- und PA-Ausprägungen mit stärkeren Konnektivitäten in Gehirnarealen wie etwa dem Precuneus und dem rechten Nucleus Caudatus, die vormalig bei Emotion, Empathie und kognitiver Kontrolle involviert waren. Alle CU-Subdimensionen korrelierten positiv mit einigen DMN und SN seedbasierten rsFC mit Clustern, die den Gyrus präcentralis, Precuneus und zerebellare Regionen beinhalteten. Diese Areale wurden mit emotionalen, empathischen, moralischen, und selbstreferenziellen Prozessen in Verbindung gebracht. Diese erste Studie zeigte somit aggressionssubtypspezifische rsFC Muster, die das Wissen über die bei Aggressionsstörungen beteiligten neuronalen Netzwerke, welche zwei Kernregionen miteinschliesst, auf spezifische Formen aggressiven Verhaltens von Kindern und Jugendlichen ausweitete.

In der zweiten Studie erweiterten wir vorherige Bestrebungen, indem wir uneingeschränkte, graphentheoretische rsFC zwischen einzelnen Voxeln im gesamten Gehirn untersuchten. Durch die Berechnung des «Intrinsic-Connectivity-Contrast» (ICC), der globalen Konnektivitätsstärke eines jeden Voxels mit allen anderen Voxeln, erfassten wir Veränderungen in der Netzwerkzentralität. Zusätzlich untersuchten wir mit der «Integrated–

Local-Correlation» (ILC) Veränderungen in lokaler Kohärenz über die Integration voxelbasierter räumlicher Korrelationen. Neben ADHD-Symptomen wurden auch komorbide Angstausprägungen berücksichtigt. Aggressive Kinder und Jugendliche zeigten nur dann abweichende rsFC im Vergleich zu gesunden Teilnehmenden, etwa im medialen Frontalkortex, wenn für Angst- aber nicht für ADHD-Symptome kontrolliert wurde. Von zentraler Bedeutung ist, dass die meisten aggressionssubtypspezifischen rsFC-Resultate innerhalb der aggressiven Studienteilnehmenden von der zusätzlichen Kontrolle für sowohl ADHD- also auch Angstsymptome abhingen. RA- und PA-Symptome standen beide in Zusammenhang mit abweichenden Konnektivitäten in parietalen Arealen und mit unterschiedlichen Konnektivitätsmustern im zentralen Gyrus und Precuneus. Diese Regionen schein bei aggressionsbezogenen, emotionalen und kognitiven Kontrollprozessen beteiligt zu sein. CU-Traits korrelierten mit Konnektivitätsmustern in temporalen und zerebralen Gehirnarealen, die mit Empathie, Emotion, und Belohnung in Verbindung gebracht werden. Diese hypothesenfreie rsFC-Studie untermauerte ebenfalls eine entsprechend den Aggressionssubtypen ausgerichtete Vorgehensweise, und betonte die zentrale Rolle des Einbezugs komorbider Symptome in ebensolchen Analysen.

Zusammenfassend weist dieses Dissertationsprojekt auf die Sensitivität von rsFC für entwicklungsbedingte Aggressionsformen hin und betont die Bedeutsamkeit, unterschiedliche Manifestationen von Aggression bei Kindern und Jugendlichen mit Störungen des Sozialverhaltens oder ausgeprägter Aggression zu berücksichtigen. Zunächst zeigten sowohl seed- als auch unbeschränkte voxelbasierte Analyseformen abweichende rsFC von aggressiven im Vergleich zu gesunden Kindern und Jugendlichen. Diese beinhaltete frontale Gehirnbereiche und hing teilweise von der zusätzlichen Kontrolle für entweder ADHD- oder Angstsymptome ab. Zum anderen zeigten beide analytischen Herangehensweisen abweichende und überwiegend spezifische rsFC in Zusammenhang mit den unterschiedlichen RA- und PA-Subtypen sowie CU-Traits innerhalb der aggressiven Studienteilnehmenden. Von zentraler Bedeutung ist die wesentliche Rolle, die komorbiden ADHD- und Angstsymptomen bei der Identifikation

aggressionssubtypspezifischer Auffälligkeiten in voxelbasierter rsFC zukam. Insgesamt zeigten diese signifikanten, sich abhängig von den Aggressionssubtypen unterscheidenden seed- und voxelbasierten Konnektivitätsmuster in einer grossen Stichprobe von aggressiven Kindern und Jugendlichen, dass verschiedene und dabei doch auch überlappende Messmethoden von Gehirnkonnektivitäten die spezifischen Formen aggressiven Verhaltens entflechten können. Darüber hinaus unterstützen diese Resultate eine dimensionale statt kategoriale Herangehensweise. Unsere Ergebnisse könnten insofern klinische Implikationen haben, als dass sie eine entsprechend den unterschiedlichen neuronalen Manifestationen von aggressivem Verhalten zugeschnittene, personalisierte Diagnostik und Behandlung von Aggressionsstörungen unterstützen.

1 General Introduction

1.1 Aggressive behavior and clinical manifestations in children and adolescents

From an evolutionary psychological perspective, there are different hypotheses on the origin of aggression. Aggression not only reflects problematic behavior but often an adapative and context-dependent way to deal with challenging situations (Buss & Shackelford, 1997). Aggression-related behavior can be understood as an attempt to deal with perceived threat or as resulting from impaired learning to inhibit instinctive fight/flight responses (Fonagy & Luyten, 2017). Physical aggression was shown to start within the first year after birth Thus, longitudinal studies started with birth cohorts and found an increasing frequency of physical aggression until the age of three to four years, which usually declines with physical growth (Tremblay, Vitaro, & Côté, 2018). However, aggression levels of most physically aggressive children show a small increase during adolescence, followed by a decrease during adulthood. Stimulation-seeking (Zuckerman & Neeb, 1979) might be an attempt of antisocial individuals to increase low autonomic arousal levels (van Goozen, Fairchild, Snoek, & Harold, 2007). From a longitudinal perspective, high levels of stimulation-seeking and fearlessness at the age of three years have been related to aggression levels eight years later (Raine, Reynolds, Venables, Mednick, & Farrington, 1998).

Aggression-related disorders in childhood and adolescence are associated with poor outcomes including criminal behavior, substance use problems, and antisocial personality disorders (Erskine et al., 2016) besides a substantial contribution to the global burden of disease (Erskine et al., 2014). There is ongoing research on developmental pathways to aggression-related disorders involving discussions on the impact of the age

of onset, for instance (Frick, 2012; Puzzo, Smaragdi, Gonzalez, Martin-Key, & Fairchild, 2016). Recent research suggests an important interplay of genetic predispositions like specific candidate genes and environmental factors including parental monitoring (Salvatore & Dick, 2016). From a clinical perspective, recurrent angry, arguing, and revengeful mood and behavior, leading to individual distress in others or negatively effect daily interactions or functioning in social environments, can manifest itself as a diagnosis as oppositional defiant disorder (ODD) in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). If three or more criteria including severe violation of norms, rules, and rights within the past year are present, a diagnosis of conduct disorder (CD) is given. ODD and CD are among the most common psychiatric disorders in childhood and adolescence with a world-wide prevalence of 5.7% (3.6% for ODD and 2.1% for CD) (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). According to the review by Waschbusch (Waschbusch, 2002), 36% of boys and 57% of girls with conduct problems have comorbid hyperactive-impulsive-inattention symptoms. Particularly the combination of an early onset of CD problems in childhood and impaired self-control is prone to a longer persistence of problematic behaviors with a peak of antisocial behavior in adolescence (Moffitt, 1993). Moreover, anxiety symptoms are frequently comorbid in children with conduct problems (Frick, 2012; Frick, Ray, Thornton, & Kahn, 2013). The effectiveness of treating aggression-related disorders in children and adolescents is small (Bakker, Greven, Buitelaar, & Glennon, 2017). As delineated in the following, a growing body of evidence elucidated the importance to differentiate between different forms of disruptive behavior.

1.2 Callous-unemotional traits and dimensions

The role of callous-unemotional (CU) traits, newly added as a specifier for CD in the DSM-5 (American Psychiatric Association, 2013), has been frequently investigated (Frick, 2016). CU traits are also named “with limited prosocial emotions” to reduce stigmatizing (Blair, Leibenluft, & Pine, 2014). Recent reviews suggested high levels of heritability (Raine, 2018) and that

CU traits might predict future antisocial behavior (Waller & Hyde, 2017), even during childhood (Dadds, Fraser, Frost, & Hawes, 2005), and adult psychopathy (Frick & White, 2008). Childhood CU traits and adult psychopathic features seem related (Frick et al., 2013; Frick & White, 2008). The interaction of inherited emotion-related deficits and fearlessness with parental practices might contribute to an increasing risk for early CU traits (Waller & Hyde, 2018). CU traits have been associated with fearlessness and higher unconcern about punishment (Fanti, Panayiotou, Lazarou, Michael, & Georgiou, 2016), impaired emotion recognition skills, particularly for fear (Muñoz, 2009; Sylvers, Brennan, & Lilienfeld, 2011), and reward-oriented behavior suggested to lead to a higher risk for most severe, frequent, and instrumental violent behavior (Reidy et al., 2017). Higher levels of CU traits related to more severe conduct problems in childhood (Longman, Hawes, & Kohlhoff, 2016) and seem to predict antisocial behavior (Dadds et al., 2005), delinquent behavior, and a diagnosis of antisocial behavior disorder in adulthood (McMahon, Witkiewitz, & Kotler, 2010). Despite stability during childhood peculiarly in fearless children (Goffin, Boldt, Kim, & Kochanska, 2017) and during adolescence (Eisenbarth, Demetriou, Kyranides, & Fanti, 2016; Frick et al., 2013; Reidy et al., 2017), CU traits tend to decrease from childhood to adolescence. As such, a minor decrease of CU traits during childhood correlated with an increased risk for externalizing problems in adolescence (Muratori et al., 2016). A recent review (Moul, Hawes, & Dadds, 2016) shed light on neurobiological alterations in children with conduct problems and CU traits. For instance, reduced functioning of the oxytocin system and serotonin neurotransmission seems related to poor emotion-recognition, which might in turn contribute to an impaired development of empathy.

In recent years, a growing body of research pointed to differentiating between dimensions of CU traits (Kimonis et al., 2008; Latzman, Lilienfeld, Latzman, & Clark, 2013; Pechorro, Ray, Gonçalves, & Jesus, 2017; Pihet, Etter, Schmid, & Kimonis, 2015) and CU-related traits (Salihovic & Stattin, 2017). Youths with CU and CU-related traits show differing anxiety levels that seem related to differential behaviors (Fanti, Demetriou, & Kimonis, 2013; Kimonis, Frick, Cauffman, Goldweber, & Skeem, 2012) like impaired

emotion recognition skills (Dadds, Kimonis, Schollar-Root, Moul, & Hawes, 2017) and higher levels of aggression-related behaviors (Fanti et al., 2013; Guelker, Barry, Barry, & Malkin, 2014).

1.3 Reactive and proactive aggression subtypes

Reactive (RA) and proactive (PA) aggression symptoms (Dodge & Coie, 1987; Vitiello & Stoff, 1997) also characterize important aspects of aggressive behavior. RA symptomatology describes aggressive reactions to internal or external provocation (Smeets et al., 2016), while PA specifies instrumental, planned aggressive behavior in order to influence others (Dodge & Coie, 1987). There is evidence for a differing heritability of RA and PA symptomatology (Waltes, Chiocchetti, & Freitag, 2016). For instance, harsh parenting has predicted both aggression forms, while negative emotionality was shown to predict RA but not PA behavior in children (Vitaro, Barker, Boivin, Brendgen, & Tremblay, 2006). High levels of RA and PA symptoms seem to increase in early and decline in late adolescence (Tremblay et al., 2018).

On the one hand, existing behavioral literature suggests a substantial correlation of the proposed RA and PA subtypes (Card & Little, 2006; Polman, Orobio De Castro, Koops, Van Boxtel, & Merk, 2007; Poulin & Boivin, 2000) and commonalities (Cima, Raine, Meesters, & Popma, 2013; Marsee et al., 2011). For instance, both have been associated with CU traits (Feilhauer, Cima, & Arntz, 2012; Kimonis et al., 2008; Pechorro et al., 2017) and CU-related traits (Blais, Solodukhin, & Forth, 2014; Perenc & Radochonski, 2014) and with increased CD symptoms and CU traits in adolescents (Eisenbarth et al., 2016). On the other hand, there is support for their differentiation on a psychophysiological (Scarpa, Haden, & Tanaka, 2010) and behavioral level. While RA behavior has been linked to impulsivity and social anxiety, PA symptoms seem related to delinquency and hyperactivity (Raine, Dodge, Loeber, Gatzke-Kopp, Lynam, Stouthamer-Loeber, et al., 2006). High levels of RA symptoms seem to increase the risk for higher internalizing problems (Fite, Rubens, Preddy, Raine, & Pardini, 2014) and related to impulsivity (Connor, Steingard, Anderson, & Melloni,

2003; Fite, Stoppelbein, & Greening, 2009; Urben et al., 2018) and suicidal behaviors (Hartley, Pettit, & Castellanos, 2016), and are thought to positively predict CU-related traits in early adolescence (Bamvita et al., 2017). In contrast, PA symptoms seem associated with reduced moral-related processes in early childhood (Jambon & Smetana, 2018), conduct problems (Smeets et al., 2016), and CU or CU-related traits (Fite et al., 2009; Marsee et al., 2011; Marsee & Frick, 2007; Urben et al., 2018; White, Gordon, & Guerra, 2015). Psychophysiological research in children (Scarpa et al., 2010) and adolescents (Gao, Tuvblad, Schell, Baker, & Raine, 2015) reported both distinct and inconsistent findings (Fanti, 2016) regarding the RA/PA-related differentiation.

Taken together, considering RA and PA behaviors seems inevitable when subtyping aggression-related disorders in children and adolescents.

1.4 Methods to study neural correlates of aggression subtypes – resting state fMRI

During magnetic resonance imaging (MRI), changes in physiological events are reflected by changes in blood-oxygen-level-dependent (BOLD) signals (Ogawa, Lee, Kay, & Tank, 1990). Studies of functional MRI (fMRI) assume that active brain regions are characterized by a local change in the amount of measured deoxygenated hemoglobin in the blood (Huettel, Song, & McCarthy, 2009). Neural activity is measured indirectly and non-invasively with good spatial resolution as the difference between oxygenated and deoxygenated blood by recording changes in the MR signal emerging as radiofrequency waves. The process of excitation is described as the application of a radio frequency pulse to protons spinning parallel to a strong magnetic field (longitudinal magnetization), which leads to high-energy states in proton spins (transverse magnetization). Stopping the pulse leads to a process of relaxation, as the protons return to a low-energy state. The time of recovering the longitudinal magnetization is called longitudinal relaxation (T1). Afterwards, the signal of transverse components decays, measured as transverse relaxation time (T2). The BOLD-contrast during fMRI is based on the time constant T_2^*, which

delineates the decay of transverse magnetization due to interactions of rotating spins precessing at higher or lower frequencies and spatial inhomogeneities in the local magnetic field (Huettel et al., 2009).

Biswal and colleagues (Biswal, Yetkin, Haughton, & Hyde, 1995) were the first describing resting state fMRI (rs-fMRI) when they detected that low-frequency time courses of brain regions during hand movement are also detectable during periods of rest, along with further regions relating to motor function. There is evidence for distinct highly functionally connected brain regions active in the absence of goal-directed behaviors, known as resting state networks (RSNs) (Damoiseaux et al., 2006; Fox, Spreng, Ellamil, Andrews-Hanna, & Christoff, 2015; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001). For instance, the default mode network (DMN) consists of a distinct set of functionally highly connected brain regions activated during rest (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Fox et al., 2015; Raichle et al., 2001) across all age groups (Mak et al., 2017) including children (Thomason et al., 2011). The connectivity strength of RSNs was shown to exhibit moderate to high test-retest reliability across subjects and runs with varying acquisition parameters (van Dijk et al., 2010). An fMRI acquisition method emerging in recent years collects multiple instead of single echo images for each slice. This allows for modelling the T_2^* signal decay for each voxel, which in turn enables to differentiate between BOLD and artifact signal (Kundu et al., 2017). For instance, the effect of motion-related noise on DMN rsFC could be minimized by using a multi-echo compared to a single-echo approach (Dipasquale et al., 2017).

There are different ways to analyze rs-fMRI data. The hypothesis-driven seed-based approach is among the most frequently applied methods for analyzing rsFC (Biswal et al., 1995; Fox et al., 2005; Greicius et al., 2003; Whitfield-Gabrieli & Ford, 2012). After a priori definition of regions of interest (ROIs), the correlation between BOLD time courses from a seed and whole-brain voxel clusters is calculated at a predefined threshold (Lee, Smyser, & Shimony, 2013). In order to further explore rs-fMRI data, unrestricted, hypothesis-free, and graph theory-based approaches include the Intrinsic Connectivity Contrast (ICC) and the Integrated Local

Correlation (ILC) (Whitfield-Gabrieli & Nieto-Castanon, 2012). ICC enables to analyze rsFC alterations in the whole brain without an a priori definition of ROIs (Martuzzi et al., 2011). Using ICC, the global correlation strength of voxel-to-voxel connectivity patterns is calculated, which measures changes in network centrality (Whitfield-Gabrieli & Nieto-Castanon, 2012). Regarding local voxel-wise rsFC patterns, ILC enables to examine changes in local coherence by integrating spatial correlations of each voxel without the need for a specified finite neighborhood for the integration, as in other local coherence approaches (Deshpande, LaConte, Peltier, & Hu, 2009).

Numerous studies provide evidence for psychiatric disorders to be associated with altered rsFC (Woodward & Cascio, 2015). Thus, studies of rs-fMRI may attribute to diagnosis and personalized treatment by exploring relations to psychiatric disorders (Barch, 2017; Whitfield-Gabrieli & Ford, 2012).

1.5 Neural alterations in aggression-related disorders

There is evidence for neural alterations on both a structural and functional level, with functional ones at rest and in tasks probing aggression-related processing. Antisocial and disruptive youths have been reported to show less punishment and higher immediate reward oriented behavior and thus deficit functioning of associated brain areas (Byrd, Loeber, & Pardini, 2014) including (pre-) frontal regions like the medial prefrontal cortex along with temporal alterations (Alegria, Radua, & Rubia, 2016). Another review and meta-analysis documented both structural and functional neural abnormalities including the left insula (Raschle, Menks, Fehlbaum, Tshomba, & Stadler, 2015). Interestingly, ADHD and disruptive behavior disorders seem to exhibit overlapping neural impairments in cognitive control networks which include the orbitofrontal cortex (OFC), cingulate, and insular cortices (Puiu et al., 2018). Given the heterogeneity within aggression-related disorders associated with different neural alterations, it is of particular concern to differentiate between the distinct manifestations and traits also on a neural level (Blair, Veroude, & Buitelaar, 2016).

1.5.1 Neural correlates of oppositional defiant and conduct disorder

In CD and ODD, disrupted functioning of frontal, striatal, and limbic regions has been associated with altered emotional, reward, and punishment processing and related regulatory mechanisms (Blair et al., 2016; Noordermeer, Luman, & Oosterlaan, 2016). For instance, besides alterations in frontal brain regions including the OFC implicated in disrupted reward-related behavior also in ADHD (Von Rhein et al., 2015), functioning of the amygdala (Holz et al., 2016) and anterior insular cortex correlated with different forms of empathic processes, which are impaired in adolescents with conduct problems (Blair et al., 2016). As reviewed recently, abnormal fear conditioning and, closely linked, punishment processing in ODD and CD have been associated with altered amygdala activity, which in turn seems implicated in reward-related processes (Matthys, Vanderschuren, & Schutter, 2013). Moreover, the impaired cognitive regulation of emotional behaviors is thought to be associated with structural and functional alterations in paralimbic regions including the OFC and cingulate cortices. A recent meta-analysis identified reduced gray matter volumes in brain regions such as left amygdala, right insula (Rogers & De Brito, 2016), and left central gyrus along with the posterior cingulate cortex (PCC) depending on the CD severity (Smaragdi et al., 2017) in youths.

During rest, many of the networks activated or deactivated in tasks can also be observed using fMRI. Recent studies in male adolescents with CD suggested mainly diminished resting state functional connectivity (rsFC) (Aghajani et al., 2017; Broulidakis et al., 2016; Lu, Zhou, Wang, Xiang, & Yuan, 2017; Lu et al., 2015; Zhou et al., 2016) and activity (Lu et al., 2015; Wu, Zhang, Dong, Wang, & Yao, 2017). For instance, male adolescents with CD demonstrated reduced rsFC between the core regions of the DMN, anterior medial prefrontal cortex (amPFC) and PCC, compared to healthy control subjects only after controlling for ADHD symptoms, as ADHD symptoms correlated positively with rsFC within the DMN (Broulidakis et al., 2016). Further studies found increased (Pu et al., 2017) but mainly reduced rsFC including areas of the DMN (Lu, Zhou, Wang, et al., 2017; Lu et al., 2015; Zhou et al., 2016) and the somatosensory network (Lu et al., 2015).

Diminished neural activity during rest in brain regions has been reported in parts of the salience network (SN) (Zhou, Yao, Fairchild, Zhang, & Wang, 2015) along with cerebellar and parietal areas (Wu et al., 2017). Another recent study in male and female patients with CD documented altered spontaneous activity including a reduced amplitude of low frequency fluctuations in left inferior/middle temporal gyrus (ITG/MTG) in males compared to females (Cao, Sun, Dong, Yao, & Huang, 2018). Impulsivity scores have been related to mainly increased rsFC in SN (Pu et al., 2017) and DMN regions (Lu, Zhou, Wang, et al., 2017; Lu, Zhou, Zhang, Wang, & Yuan, 2017; Shannon et al., 2011) also found in boys with CD and ADHD (Uytun et al., 2016).

In sum, most of rs-fMRI studies to date exclusively included male adolescents with CD, had sample sizes for cases of $N < 60$, differing methodological approaches, and disregarded distinct heterogeneous manifestations of aggression-related disorders such as RA and PA symptomatology. This makes it difficult to draw reliable conclusions on rs-fMRI-derived neural alterations children and adolescents.

1.5.2 Neural correlates of callous-unemotional traits

Youths presenting with CU traits have been characterized by reduced functioning of brain regions related to reinforcement and emotional empathy, such as amygdala (Blair et al., 2014; Herpers, Scheepers, Bons, Buitelaar, & Rommelse, 2014) and anterior insula (Michalska, Zeffiro, & Decety, 2016; Reidy et al., 2017). A recent study reported that CU traits predicted a reduced cingular-limbic functional connectivity when viewing harm to others (Yoder, Lahey, & Decety, 2016), while in another study CU traits correlated with reduced cingular response to fearful faces (Szabó et al., 2017). Psychopathic traits in adulthood have been associated with (para-)limbic abnormalities (Kiehl, 2006) and the amygdala has been suggested as core region (Blair, 2017). However, there is growing evidence for neural alterations beyond (para-)limbic regions (Griffiths & Jalava, 2017). On a structural level, CU traits related to alterations in temporal regions (Cohn et al., 2016; Fairchild et al., 2015; Wallace et al., 2014) along

with frontal (Fairchild et al., 2013; Umbach, Berryessa, & Raine, 2015) and parietal areas (Yang et al., 2015).

Only a limited number of rsFC studies considered CU traits in children and adolescents, thereby mostly including male adolescents with CD. There are reports of CU and CU-related dimension-specific increases in regions of the DMN (Cohn et al., 2015; Thijssen & Kiehl, 2017) along with the SN and other resting state networks (RSNs) (Thijssen & Kiehl, 2017). Juvenile offenders with CD and differing levels of CU(-related) traits were shown to exhibit differing rsFC patterns including clusters in fronto-limbic and fronto-parietal areas (Aghajani et al., 2016, 2017). Likewise, there is evidence for psychopathic traits in adults to be considered. For instance, incarcerated male adults exhibited altered connectivity in multiple RSNs related to the interpersonal/affective factor of psychopathy (Espinoza et al., 2018). Another study reported an increase and decrease of rsFC depending on the psychopathic trait in brain regions including anterior insula and PCC (Philippi et al., 2015). Despite behavioral evidence for the crucial, moderating role of co-occurring anxiety levels on a behavioral level (Fanti et al., 2013), only one rsFC study considered these and documented an interaction effect of anxiety and psychopathy levels in adults (Motzkin, Newman, Kiehl, & Koenigs, 2011).

1.5.3 Neural correlates of reactive and proactive aggression

To date, few magnetic resonance imaging (MRI) studies have taken RA and PA manifestations of aggression into account. RA symptomatology might result from failed inhibition of aggressive impulses by executive brain systems (Blair, 2001). Blair (Blair, 2016) suggested frontal areas and the anterior insula cortices involved, which in turn might be implicated in reinforcement-based decision-making. Furthermore, RA behavior is thought to be mediated by the so-called acute threat response system. This neural circuit includes amygdala, hypothalamus, and periaqueductal gray, and seems modulated by prefrontal areas like the OFC (Blair, 2004; Blair, 2010). According to a recent review of fMRI studies on RA symptomatology, pathological aggression has been suggested to be associated with

hyperresponsivity in emotion-related neural circuits including the amygdala and insula and hyporesponsivity in an emotion regulation circuitry that comprises cingular and parietal areas like the precuneus (Fanning, Keedy, Berman, Lee, & Coccaro, 2017). Children with CD symptoms were shown to exhibit a positive correlation between posterior insula response to emotional empathy stimuli and RA scores (Michalska et al., 2016). With respect to PA symptomatology, amygdala dysfunction might contribute to impaired development of moral-related behaviors (Blair, 2004). Yet, there is evidence that both RA and PA symptoms might relate to altered amygdala functioning. For instance, a reduced amygdala response to fear in children with high CU traits predicted PA levels (Lozier, Cardinale, VanMeter, & Marsh, 2014). During rs-fMRI, male adult offenders exhibited a positive correlation between RA and PA scores and increased left amygdala rsFC with medial prefrontal cortex, and a RA symptoms-related decrease of left amygdala rsFC with right posterior insula (Siep et al., 2018). Furthermore, higher levels of PA and CU-related traits in adolescence have been associated with lower right amygdala volume in adulthood (Pardini, Raine, Erickson, & Loeber, 2014).

To the best of our knowledge, no rsFC study in aggressive children and adolescents examined the role of RA and PA subtypes to date.

1.6 Aims and hypotheses

This dissertation project aimed to extend the knowledge of aggression-related neural networks to distinct subtypes of aggression using rs-fMRI data derived from children and adolescents in a multi-center study. To date, studies investigating rsFC in aggressive youth restricted analysis predominantly to male adolescents with pure CD. Hence, little is known about further and specific manifestations of aggression. Particularly RA and PA subtypes along with comorbid ADHD and anxiety symptoms have been widely neglected. The current thesis attempted to fill these gaps in literature. We thus investigated rsFC in male and female children and adolescents with aggressive behavior in the clinical range including diagnoses of CD/ODD compared to controls thereby considering comorbid

symptoms. Most notably, we aimed to elucidate connectivity alterations related to RA and PA symptoms along with CU traits within cases.

In a first study, we investigated seed-based rsFC with whole-brain voxel clusters using literature-based a priori defined ROIs within the DMN and the SN. We expected reduced seed-based connectivity in cases compared to healthy controls. We considered comorbid ADHD symptoms and assumed an increase in rsFC with higher ADHD scores. Furthermore, we hypothesized that CU subdimensions would be associated with distinct and increased rsFC within cases. For RA and PA symptomatology, we tentatively speculated to find differing rsFC patterns particularly for amygdala and anterior insula seeds.

In a second study using the same sample and data, we extended previous efforts by using hypothesis-free voxel-to-voxel whole-brain approaches. ICC was employed to assess changes in global correlation strength and ILC to calculate alterations in local coherence. For all analyses, we took into account both comorbid ADHD and anxiety symptoms and expected them to partly modulate (enhance or suppress) aggression-related connectivity patterns. We hypothesized that voxel-wise rsFC alterations are found in cases compared to controls, and that these include a reduced recruitment of frontal areas. Within cases, we expected to find patterns including the precuneus related to RA and PA symptoms along with further temporal, parietal, and frontal regions associated with CU traits beyond (para-)limbic regions.

2 Study A

AGGRESSION SUBTYPES RELATE TO DISTINCT RESTING STATE FUNCTIONAL CONNECTIVITY IN DISRUPTIVE CHILDREN AND ADOLESCENTS

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Running title: Aggression subtype-specific connectivity

Keywords: reactive and proactive aggression, callous-unemotional traits, default mode network, amygdala, functional connectivity

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3 Study B

DIFFERENT WHOLE-BRAIN FUNCTIONAL CONNECTIVITY CORRELATES OF REACTIVE-PROACTIVE AGGRESSION AND CALLOUS-UNEMOTIONAL TRAITS IN DISRUPTIVE CHILDREN AND ADOLESCENTS

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Short title: Whole-brain aggression-related connectivity

Keywords: reactive aggression; proactive aggression; callous-unemotional traits, fMRI; resting state; functional connectivity; anxiety; ADHD; children; adolescents

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4 General Discussion

In this dissertation project, we investigated connectivity alterations during rs-fMRI in children and adolescents with clinical levels of aggression, and mostly with diagnoses of CD and/or ODD, compared to typically developing healthy controls. Given the limited knowledge of neural correlates underlying partly distinct manifestations of aggressive behavior at rest, particularly RA and PA symptomatology, we extended previous studies by elucidating rsFC related to these aggression subtypes along with CU traits. Both seed-based analysis (study A) and voxel-to-voxel approaches (study B) revealed rsFC alterations in cases compared to healthy controls and, most importantly, predominantly distinct aggression subtype-specific patterns. Furthermore, these results emphasized the importance of considering also clinical symptoms beyond aggression, like comorbid ADHD and anxiety symptoms. After the discussion of our findings including potential directions for future studies, implications for the clinical practice regarding the eligibility of rsFC patterns as a biomarker for aggression-related behaviors are outlined.

4.1 Resting state fMRI in aggressive children and adolescents – main findings and future directions

Investigations of rs-fMRI, which detect correlated low-frequency time courses of brain activity during periods of rest, have the advantages of being non-invasive, providing a good spatial resolution (Huettel et al., 2009), and being independent of higher levels of cooperation (Smitha et al., 2017) which facilitates rs-fMRI data collection in our population of aggressive children and adolescents. Yet, as our cases with externalizing disorders including comorbid ADHD symptoms showed higher levels of motion compared to the healthy controls, we used a threshold for excessive motion

recently applied (Pruim, Mennes, Buitelaar, & Beckmann, 2015) also in rs-fMRI analyses in adolescents with ADHD (von Rhein et al., 2016). Above that, we conducted sensitivity analyses controlling for effects of this motion parameter, which yielded comparable statistics in our case-control differences in rsFC. Despite growing research on behavioral and psychophysiological levels, neural studies of rs-fMRI in aggressive children and adolescents have widely neglected the differentiation between distinct manifestations of aggressive behavior, particularly RA and PA symptomatology along with comorbid ADHD and anxiety symptoms. Besides addressing this gap in literature, the present PhD project further extended previous research by not exclusively including male adolescents with CD but also females, children, and individuals with ODD and/or aggressive behavior in the clinical range, and providing a considerably larger sample size (N = 207) including 118 cases.

Both our seed and voxel-based rsFC findings showed that RA and PA symptoms related to predominantly distinct connectivity patterns. However, we found a converging left amygdala seed-based pattern with precuneal areas and similar voxel-wise rsFC changes including superior parietal regions related to both RA and PA symptoms. Moreover, RA and PA scores were highly correlated in our sample in line with the literature (Cima et al., 2013). These neural and behavioral similarities involving the amygdala as core region implicated in aggression might challenge the proposed distinction between RA and PA aggression subtypes. However, this amygdala seed-based pattern extended to different cingulate and occipital areas for PA and RA scores, respectively, RA scores only related to further seed-based patterns, and both forms of aggression correlated with distinct voxel-wise connectivity alterations. These RA and PA-specific results thus corroborate behavioral studies reporting differential behavioral correlates for RA and PA symptomatology (Fite et al., 2008, 2010; Marsee et al., 2011; Marsee & Frick, 2007).

Additionally, both studies revealed that the left anterior insula is implicated in CU traits-related rsFC alterations. Adults with psychopathic traits exhibited rsFC alterations including the anterior insula (Philippi et al., 2015), which might point to developmental aspects for this brain area given

that CU traits in childhood and psychopathic traits in adulthood correlate on a behavioral level (Frick et al., 2013). Moreover, some of the brain regions involved in the CU traits-related connectivity patterns reported in our studies have been linked to rsFC alterations in adults with psychopathic traits, such as the precuneus (Motzkin et al., 2011; Philippi et al., 2015) and central and angular gyrus (Espinoza et al., 2018). Furthermore, our results showed CU trait-specific rsFC alterations beyond (para-) limbic areas in frontal, parietal, cingulate, and cerebellar regions, which points in the direction of a recent review that reported broader brain areas related to psychopathy in adulthood (Griffiths & Jalava, 2017). Additionally, in both aggressive children and adolescents of our sample and in adult violent offenders of a recent study (Siep et al., 2018) RA and PA scores related to left amygdala seed-based rsFC. Thus, longitudinal studies could identify developmental trajectories by observing rsFC in these specific brain regions over time. These investigations might clarify whether these deviations reflect early onset aggressive symptoms that persist into adulthood or whether they predict future aggression-related outcomes. In both cases, designing early neurobiological interventions specifically targeted to alter connectivity patterns including these areas might be promising, as they could eventually improve behavioral outcomes. For instance, the anterior insula has been shown to be implicated during self-regulation in real-time fMRI neurofeedback (Emmert et al., 2016) and has already been targeted in adult psychopaths (Sitaram et al., 2014). Moreover, as changes in electrodermal activity were shown to involve activity in brain regions including the insular cortices (Nagai, Critchley, Featherstone, Trimble, & Dolan, 2004), arousal-biofeedback training (Schoenberg & David, 2014) may be promising and is thus part of our Aggressotype project.

Interestingly, we found some regions implicated in both RA/PA symptoms and CU traits-related rsFC. For instance, seed-based analyses showed that clusters including precentral gyrus and precuneus were implicated in both RA/PA symptoms-related patterns and those associated with CU subdimensions. Additionally, voxel-wise patterns related to RA and PA symptoms included parietal regions such as the angular gyrus, previously linked to CU traits-related activity alterations (Anderson et al., 2017). Yet,

voxel-wise and seed-based RA and PA symptoms-specific rsFC patterns in the present dissertation differed from those associated with CU traits. This contradicts previous behavioral reports of a correlation between RA and PA symptoms with CU traits (Urben et al., 2018) and the correlation of PA symptoms and CU traits in our sample according to behavioral measures. The RA and PA symptoms-specific rsFC results differing from the CU traits-related findings thus add further evidence to the knowledge of distinct underlying neural correlates for these manifestations of aggression.

Additionally, our findings strongly suggest that research (and clinical practice) should consider comorbid symptoms in disruptive children and adolescents given that these comorbidities exert suppressor effects on numerous rsFC patterns. Thereby, the reduced seed-based limbic-frontal rsFC in cases compared to controls depended on the additional control for ADHD symptoms, and the voxel-based connectivity alterations including the medial frontal cortex vanished without the additional control for anxiety problems. Above that, most voxel-based rsFC subtype-specific alterations within cases could only be identified when both ADHD and anxiety symptoms were considered. This provides support for previous neural studies regarding ADHD symptoms in rsFC within the DMN in male adolescents with CD (Broulidakis et al., 2016), and regarding anxiety levels in rsFC (Motzkin et al., 2011) and task-based fMRI (Sethi, Sarkar, et al., 2018) in psychopathic adults. In our studies, we extended these findings to brain regions like the SN and to further aggression subtypes including RA and PA symptomatology. The behavioral correlations, particularly within cases, provide further support for correlations between anxiety and both RA and PA symptoms (Fite et al., 2014; Fung et al., 2015) or with RA symptoms particularly (Marsee et al., 2008; Vitaro et al., 2002) in previous behavioral studies. Our rsFC results also corroborate behavioral research emphasizing the crucial role of both ADHD (Fonagy & Luyten, 2017) and anxiety symptoms (Frick, 2012; Frick et al., 2013) in disruptive children and adolescents. A recent longitudinal study documented a negative association between anxiety and CU-related traits at age six and, beyond that, anxiety levels predicting CU-related traits six years later (Bamvita et al., 2017). Another dimensional severity-based approach found that youths with both

high CU traits and high compared to low levels of anxiety differ in factors, such as a more severe trauma history in childhood and ADHD symptoms (Cecil, McCrory, Barker, Guiney, & Viding, 2018). CU traits combined with high levels of anxiety further related to distinct characteristics like increased aggression and conduct problems (Fanti et al., 2013) as in our sample, along with reduced self-reported cognitive empathy (Kahn, Frick, Golmaryami, & Marsee, 2017), increased antisocial behavior and peer problems (Humayun, Kahn, Frick, & Viding, 2014). On the contrary, increased CU traits in youths with low anxiety levels related to reduced emotion recognition skills (Dadds et al., 2017), emotional intelligence (Kahn, Ermer, Salovey, & Kiehl, 2016), perceived positive outcomes of antisocial behavior and higher participation in these behavior (Guelker et al., 2014), and emotion-related deficits (Kimonis et al., 2012). Given this growing body of literature on a behavioral level, it is somehow surprising that rsFC analysis to date neglected the role of comorbid anxiety symptoms and only few considered co-occurring ADHD symptoms.

Furthermore, both analysis approaches showed that cases and controls differed only in few rsFC patterns leaving limited room for interpretation, as the differences only survived the correction for site but not for further covariates including sex, IQ, handedness, and medication. In contrast, we observed several dimensional aggression subtype-specific results within cases derived from both seed and voxel-based analyses, which broadly survived additional corrections. This point to the heterogeneity within aggression-related disorders and, above that, support rather a dimensional than categorical approach as increasingly promoted in recent years (Blair et al., 2016; Wesselhoeft et al., 2018).

In contrast to the majority of previous rsFC-studies, our projects included not only male but also female participants. The distribution of sex in our sample reflected prevalence estimates, for instance regarding CD (Loeber, Burke, & Pardini, 2009). Yet, from a statistical point, the smaller number of female patients with aggressive behavior in the clinical range (N = 19) compared to male cases (N = 99) and, above that, recruited from different sites, makes it statistically difficult to draw reliable conclusions on sex-related effects. As recently documented, adolescents with CD showed sex-

related differences in spontaneous brain activity during rest including left ITG/MTG (Cao et al., 2018). In our sample of aggressive boys and girls, comparable temporal regions exhibited CU traits-related changes in voxel-wise patterns, which survived the post hoc control for additional covariates including sex. Nevertheless, we included this variable as a covariate and conducted corresponding sensitivity analyses. However, future studies could elucidate sex-related differences in aggression subtype-specific rsFC.

Regarding the applied statistical approaches, we decided to use a seed-based approach with whole-brain voxel clusters on the one hand and voxel-to-voxel graph-theory-based unrestricted whole-brain analyses on the other hand. The common seed-based approach (Aghajani et al., 2016, 2017; Pujol et al., 2012; Uytun et al., 2016) provides us with information of brain areas functionally connected with a seed and a direct interpretation of the results (Mak et al., 2017). While ICA enables to identify spatially distinct RSNs (Beckmann, DeLuca, Devlin, & Smith, 2005), seed-based analysis do not require to manually select important components and to distinguish between noise and physiological signal (Lee et al., 2013). Moreover, results of ICA and seed-based analysis seem comparable (Rosazza, Minati, Ghielmetti, Mandelli, & Bruzzone, 2012). Our second study included the calculation of both global (ICC) and local (ILC) voxel-wise connectivity changes. ICC has been frequently applied in recent rsFC studies (Browndyke et al., 2018; Cassady et al., 2018; Van Ombergen et al., 2017; Vatansever et al., 2017; Walpola et al., 2017) and is used to calculate the global connectivity strength and determine degree or network centrality (Martuzzi et al., 2011). Among the advantages of ICC is the circumvention of the need for a priori definitions of ROIs, as required for seed-based analysis. ILC integrates spatial correlations to calculate average local connectivity patterns and provides us with an independence of image resolution and no need for predefining the neighborhood, as necessary for other local coherence approaches such as regional homogeneity (Deshpande et al., 2009). Given our considerable larger data set, it would be of great interest to determine rsFC patterns by using classification methods (Abós et al., 2017), as recently applied to identify levels of psychopathology in children and adolescents (Sato et al., 2018) and on a structural level to distinguish

male adolescents with conduct disorder from healthy controls (Zhang et al., 2018). This approach could enable to elucidate connectivity patterns related to aggression subtype-specific behavioral measures, which might provide further support for an aggression subtype-specific approach.

Furthermore, one has to keep in mind that MRI-derived data provides a good spatial resolution, but data collected with other imaging methods like the electroencephalogram (EEG) provides a higher temporal resolution (Huettel et al., 2009). Thus, in order to widen the knowledge of aggression-related neural correlates with both a good location of the signal and more precise information regarding oscillations of brain activity (Huettel et al., 2009; Meyer-Lindenberg, 2010), future studies could investigate connectivity alterations during task-based fMRI paradigms combined with EEG measures.

For this dissertation, data collection took place at nine sites across Europe using differing scanners with partly diverging scan parameters. Implementing a multi-echo resting state sequence at all participating sites would have further improved the differentiation between BOLD and artifact signal (Kundu et al., 2017). In order to control for site effects, we added a dummy-coded site covariate in all rsFC analyses, as sensitivity analyses revealed a significant effect of site on some rsFC patterns. However, we collected data from travelling heads at each site and defined consistent inclusion and exclusion criteria, which included standard clinical measures. Above that, activation variability due to site specific variations has been shown to be small in other studies (Yendiki et al., 2010), and recent multi-centric rs-fMRI-studies successfully analyzed data from multiple sites (Biswal et al., 2010; Chen et al., 2016; Jovicich et al., 2016; Tomasi & Volkow, 2012). Moreover, the larger sample size and multi-center design might improve reliability and generalizability of our results. Despite these advantages, we did not explicitly account for potential effects based on cultural differences. Yet, there is evidence for systematic mechanisms to affect the assessment of child problem behavior vary across cultural minorities, as members of some cultures might tend to report aggressive behavior to a lesser extend (Eisner & Ribeaud, 2007). Furthermore, a recent paper points to the importance of considering the role of social norms

regarding neurobiological differences of aggression (Porter, 2018). Consequently, future studies could address cultural differences by systematically document cultural origins of the participants in order to control potential culture-related differences and increase generalizability of aggression-related correlates.

With respect to interpretation of the observed rsFC results, there are some limitations worth mentioning. The number of rs-fMRI studies in aggressive children and adolescents is limited, mostly restricted to male adolescents with CD exclusively, characterized by differing methodological approaches, and with respect to RA and PA subtypes and comorbid anxiety symptoms non-existent. This made it considerably difficult to embed and interpret the observed rsFC patterns in the present PhD project. Noteworthy, some of these previous rs-fMRI studies used the same sample of male adolescents with CD and healthy controls five times (Lu, Zhou, Wang, et al., 2017; Lu, Zhou, Zhang, et al., 2017; Lu et al., 2015; Zhou et al., 2016, 2015). This might elucidate the knowledge of implicated brain areas revealed by differing methodological approaches though hardly enables transferring these results to a broader population of patients with aggression-related disorders. Therefore, we tentatively linked altered functioning during rest observed in our sample of aggressive children and adolescents to results reported in similar brain regions in task-based functional and structural MRI studies.

Moreover, it is important to note that rs-fMRI data in general does not allow for conclusions on brain activity or connectivity in response to stimuli or during a specific task to be drawn. Compared to task-based fMRI, though, rs-fMRI has many advantages. For instance, it provides us with an improved signal-to-noise-ratio, enables investigating a considerable number of brain functions by applying different analyses approaches while using the same data set, and is independent of higher levels of cooperation as needed for task-based designs (Smitha et al., 2017). Moreover, RSNs like the DMN (Andrews-Hanna et al., 2010; Fox et al., 2015; Raichle et al., 2001) can be identified during rs-fMRI across all age groups (Mak et al., 2017) including children (Thomason et al., 2011), and rsFC patterns were shown to exhibit

moderate to high test-retest reliability across subjects and sessions (van Dijk et al., 2010).

Yet, evidence from aggression subtype-specific structural and task-based functional MRI is inevitable to draw further conclusions that might eventually effect diagnostic and treatment approaches. To date, these interventions designed to treat aggression-related disorders in children and adolescents show small effect sizes (Bakker et al., 2017) and seem to be less effective in the presence of CU traits (Wilkinson et al., 2016). There are suggestions that children and adolescents with high levels of CU traits might profit from interventions that consider environmental factors such as parenting practices (Fonagy & Luyten, 2017) and, broadly speaking, from an individualized treatment according to the distinct manifestation of aggression (Frick, 2016). For instance, there is evidence for a better response in children with conduct problems and additional CU traits to emotion-recognition-training (Dadds, Cauchi, Wimalaweera, Hawes, & Brennan, 2012). The results documented in the present PhD project encourage transferring an aggression subtype-specific approach to the clinical practice. Thus, diagnostic and treatment approaches might not only profit from considering CU-traits (Umbach et al., 2015; Wilkinson et al., 2016) but also to RA and PA along with comorbid ADHD and anxiety symptoms.

Taken together, our results shed light on aberrant rsFC patterns in aggressive children and youths compared to healthy controls and on the essential role of distinct manifestations of aggressive behaviors including comorbid ADHD and anxiety symptoms within cases. Besides several limitations, such as possibly lowered study power due to partly deviating scan parameters, the reasonable larger sample size and multi-center design are among the strengths of our studies, as they may increase reliability and generalizability of the reported results. The rsFC analyses conducted in the present PhD project and the resulting aggression-related connectivity patterns add to further characterizing and disentangling task-independent neural correlates of different aggressive behaviors in children and adolescents. Future studies could reveal aggression-related connectivity patterns at a higher temporal resolution by applying EEG measurements

during task-based designs. Longitudinal designs might clarify the role of aggression subtype-specific neural correlates such as amygdala and insula over time, with promising implications for early interventions.

4.2 Clinical implications – functional connectivity alterations during rest as a biomarker in disruptive children and adolescents?

The present PhD project investigated aggression-related connectivity aberrations during rs-fMRI in children and adolescents. Our main aim was to understand neural alterations related to distinct forms of aggression, particularly RA and PA symptomatology along with CU traits. Both studies revealed aggression subtype-specific rsFC patterns, thereby extended the knowledge of aggression-related neural networks to distinct aggression subtypes. Beside these new insights, our results further underlined the crucial role of considering ADHD and anxiety symptoms, frequently comorbid in aggression-related disorders though widely disregarded to date.

Neuroimaging studies could extend the knowledge of underlying mechanisms, design tailored treatment, and investigate treatment effects (Umbach et al., 2015). Hence, clinicians would be able to not only tailor treatment accordingly but also monitor progress and evaluate the effects of interventions (Puzzo et al., 2016). Using rs-fMRI in particular, patients with psychiatric diagnoses, such as major depressive disorder, autism, or ADHD, have been distinguished from controls (Lee et al., 2013). Given advantages like the relatively ease of acquiring rs-fMRI data, rs-fMRI-derived patterns might be a promising future biomarker and additional diagnostic tool for psychiatric disorders (Woodward & Cascio, 2015), also in children (Thomason et al., 2011). Using research of the Human Connectome Project and further large databases could facilitate linking behavioral characteristics to rsFC patterns (Woodward & Cascio, 2015). The potential use of rsFC alterations as a biomarker in children and adolescents with

aggressive behavior in the clinical range, accompanied by several challenges and limitations, will be outlined in the following.

Amid the heterogeneity of aggression-related disorders with diverging implications for treatment (Byrd et al., 2014; Umbach et al., 2015; Wilkinson et al., 2016), the need for investigating aggression subtypes is evident. To address the variety in aggression-related disorders, the Research Domain Criteria (RDoC) approach is of particular interest, as it integrates different domains (Fonagy & Luyten, 2017) and considers mental disorders in the light of dysfunctions in neural circuits (Insel et al., 2010). Moreover, given the growing body of evidence of dysfunctional neural systems in aggression-related disorders including limbic, paralimbic, and frontal areas associated with cognitive impairments (Blair et al., 2016), the RDoC approach might be useful. Thus, syndromes could be characterized based on the identification of underlying trajectories on different levels including neuroimaging, which would optimize diagnostic and treatment as defined by precision psychiatry (Silbersweig & Loscalzo, 2017). A recent paper integrated theoretical approaches and empirical findings regarding aggression and conduct problems from the RDoC perspective, and underlines the importance of considering biological, psychological, and environmental factors (Fonagy & Luyten, 2017). For instance, the authors identified impaired empathic responses and emotional perspective taking as relevant etiological factors, and two main clusters of children and adolescents with high anxious, reactive aggressive behaviors on the one side and impaired affective mentalizing, instrumental form of aggression on the other side. These RDoC-derived findings corroborate our observed distinct RA and PA symptoms-related rsFC patterns along with the crucial role of considering co-occurring anxiety symptoms.

The RDoC approach, though, is accompanied by several challenges. For instance, one important challenge is to consider the differing outcomes related to the same diagnosis, as reflected by the heterogeneity within conduct disorder. Therefore, distinct factors can lead to similar rsFC profiles (Lilienfeld, 2014). In CD, there is evidence for genetic and environmental factors and gene-environment interplays (Salvatore & Dick, 2016). For instance, trauma history has been shown to play an important role in

differentiating CU youths with high and low anxiety levels (Cecil et al., 2018), and childhood family adversity including poor parental monitoring seems to predict structural and functional alterations in young adults in brain areas like the amygdala (Holz et al., 2016). Regarding rs-fMRI, early-life stress exposure in young children seems related to higher regional homogeneity during rs-fMRI in the left lateral frontal cortex (Demir-Lira et al., 2016). Therefore, a holistic and comprehensive understanding of rsFC patterns as possible biomarker for aggression-related disorders seems inevitable. Thus, we need to consider not only biological predispositions but also whether these predispositions effectively resulted in disruptive behavior (Lilienfeld, 2014). This might be of high relevance to inform subsequent targeted therapeutic interventions accordingly. In sum, the RDoC approach could enable to capture and determine the heterogeneity of psychiatric disorders including clinical manifestations of aggression-related disorders (Fonagy & Luyten, 2017). Given its limitations, particularly regarding the equifinality of differing developmental pathways with diverging implications for treatment, this framework might be of rather supplemental utility (Lilienfeld, 2014).

Furthermore, information about developmental trajectories derived from longitudinal studies might contribute to determining specific rsFC patterns as biomarker for aggression-related disorders and their distinct subtypes and manifestations in childhood and adolescence. At the same time, possible maturation-related changes in rsFC (Thomason et al., 2011; van Dijk et al., 2010) would have been taken into account, for instance in prefrontal and precuneal areas (Chen et al., 2015).

Moreover, the differing analysis methods in the present and in previous studies need evaluation regarding their efficacy in identifying psychiatric symptomatologies (Lee et al., 2013). It is noteworthy though that the different methodological approaches applied in our studies revealed partly overlapping brain regions implicated in rsFC alterations. For instance, both analysis methods showed PA-related connectivity alterations in precuneal areas. The precuneus has been associated with cool executive functioning, which describes behaviors such as self-regulation (Diamond, 2013). Interestingly, a recent narrative review reported reduced precuneal activity

linked to ODD/CD (Noordermeer et al., 2016). Moreover, a recent meta-analytic study related trait aggression and executive functioning to aberrant brain activity including the precuneus (Wong et al., 2018). Beside the PA-related precuneal patterns, case-control differences including the frontal pole and CU traits-related rsFC alterations including the left insula within cases resulted from both seed and voxel-based analysis. Therefore, these areas might be of high relevance for subtyping aggressive behavior on a neural level.

Finally, in order to use rsFC patterns as a predictive biomarker in aggression-related disorders and their distinct manifestations, future research is needed to replicate our findings particularly regarding RA and PA aggression subtypes and comorbid anxiety symptoms, as they have been investigated in this PhD project for the first time in the field of rs-fMRI. Taken together, the aggression subtype-specific rsFC patterns documented here showed that differing analysis approaches – revealing similar subtype-specific areas implicated like the left anterior insula and the precuneus – can enable to disentangle distinct manifestations of aggressive behaviors. Thus, these patterns might be promising neuroimaging biomarkers in children and adolescents with disruptive behavior.

4.3 Conclusions

In this PhD project, we applied two analysis approaches to investigate aggression-related aberrations of brain function at rest in a rs-fMRI sequence acquired from a relatively larger sample ($N > 200$) of children and adolescents recruited in the framework of the European multi-center projects Aggressotype/MATRICS. First, cases showed both seed and voxel-based connectivity alterations in brain areas including the frontal pole compared to healthy controls. These group differences partly depended on the additional control of co-occurring ADHD or anxiety symptoms respectively. Second, both studies revealed predominantly distinct RA and PA symptoms-related rsFC alterations in brain areas including the precuneus along with CU traits-related patterns involving the left anterior insula within cases. Third, particularly the observed aggression subtype-

specific voxel-wise results emphasized the importance of additional considering both comorbid ADHD symptoms and anxiety levels.

This dissertation points to the importance of differentiating between RA and PA symptoms and CU traits in children and adolescents with aggressive behavior in the clinical range on a neural level. Moreover, considering comorbid levels of ADHD and anxiety seems inevitable. Our results add to the knowledge of neural characteristics implicated in different aggression-related behaviors and their specific clinical manifestations. The present PhD project further encourages a careful assessment of distinct manifestations of aggressive behaviors and comorbid symptoms following clinical standards and guidelines as well as using additional research instruments. Our results might be promising predictive biomarkers for specific forms of aggression in children and adolescents. Above that, they may eventually inform improved diagnostic and treatment of aggression-related disorders thus tailored accordingly, as already implemented in the individualized arousal-biofeedback training in our Aggressotype project.

Abbreviations

ADHD	attention deficit/hyperactivity disorder
amPFC	anterior medial prefrontal cortex
BOLD	blood-oxygen-level dependent
CD	conduct disorder
CU	callous-unemotional
DMN	default mode network
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
FDR	false discovery rate (correction)
fMRI	functional magnetic resonance imaging
FWE	family-wise error (correction)
GLM	generalized linear model
ICC	intrinsic connectivity contrast
ILC	integrated local correlation
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
ODD	oppositional defiant disorder
OFC	orbitofrontal cortex
PA	proactive aggression
PCC	posterior cingulate cortex
RA	reactive aggression
ROI	region of interest
RDoC	research domain criteria
rsFC	resting state functional connectivity
rs-fMRI	resting state functional magnetic resonance imaging
RSN	resting state network

SN salience network

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